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(optical adj1 isomer\$) same activ\$ same ether	116

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L3: Entry 61 of 116

File: USPT

Jan 8, 1980

DOCUMENT-IDENTIFIER: US 4182902 A

TITLE: Novel cholesterol-lowering compounds

Brief Summary Text (15):

As previously indicated, with certain of the compounds according to the invention, A.sup.1 and A.sup.2 may be different so that the carbon atom linking A.sup.1 and A.sup.2 is asymmetric. For this purpose, two groups A.sup.1 and A.sup.2 are to differ in their carbon atom content such that the total carbon atom content of the two alkyl groups is not more than 10. Thus A.sup.1 and A.sup.2 can be methyl, ethyl, n-propyl or isopropyl, n-butyl isobutyl or t-butyl or any of the pentyl, hexyl, heptyl, octyl or nonyl groups. The alkyl groups preferably contain from 1 to 4 carbon atoms. The nature of the optical isomerism based on the carbon atom linking the ether oxygen atom and the carboxyl group is not critical. Both D- atom and L- forms of the compounds as well as racemates thereof possess hypocholesterolemic and hypolipemic activity.

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L5: Entry 38 of 65

File: USPT

Oct 27, 1998

DOCUMENT-IDENTIFIER: US 5827836 A

TITLE: Retinoid glycerol phospholipid conjugates

Abstract Text (1):

Retinoyl substituted glycerophosphoethanolamines are disclosed having the general Formula I: ##STR1## wherein one of A, B or C is a fatty ether substituent, one is a natural or synthetic retinoid ester substituent, and one is a phosphoethanolamine substituent, provided that A, B and C are each a different substituent. The optical and geometric isomers of compounds of Formula I and the pharmaceutically acceptable salts of the compounds, including the isomers, are also disclosed. The compounds (including the isomers thereof) and salts of the invention exhibit anti-tumor, anti-psoriatic and anti-inflammatory activities.

Brief Summary Text (5):

Synthetic fatty alkyl and alkenyl ether glycerophospholipids with potential anti-tumor properties are reported in the literature, for example, see F. Paltauf and A. Hermetter, Methods in Enzymology, 197, 134-149 (1991). The particular compound, 1-O-octadecyl-2-O-methyl-sn-glycero-3-phosphocholine (ET 18-OCH.sub.3), has markedly potent anti-tumor activity, see R. Andreesen, "Ether Lipids in the Therapy of Cancer", Prog. Biochem. Pharmacol., 22, 118-131 (Karger, Basel 1988). Treatment of cancer with a fatty alkyl ether glycerophosphoethanolamine component is also disclosed in U.S. Pat. No. 4,372,949. Halo substituted cytostatic analogs are described by H. Brachwitz et al., Chemistry and Physics of Lipids, 31, 33-52 (1982). Glycero-phosphoethanolamines bearing a non-cyclic NR.sub.1 R.sub.2 substituent in the 2-position and a lower C.sub.1-5 alkyl ether substituent in the 1-position are disclosed in U.S. Pat. No. 5,116,992. Applicants are unaware, however, of the hereinafter described fatty alkyl and alkenyl ether glycerophosphoethanolamines bearing a retinoyl substituent.

Detailed Description Text (38):

The compounds of Formula (I) have an asymmetric carbon atom (C2 position in the glyceryl backbone) in their structure and consequently they may exist in the form of different R and S optical isomeric forms (enantiomers) or racemates. Substantially pure forms of the R-and S-isomer may be obtained, substantially free of the other, by the application of art-known resolution methodologies such as, for example, by selective crystallization or by column chromatography, or by starting their preparation from the R- or S-isomer of an appropriate precursor, for example, the starting Compound (A) shown in Reaction Scheme I.

Detailed Description Text (43):

The compounds of formula (A) are known in the literature or are obtainable by art recognized procedures, for example, see A. Hermetter and F. Paltauf, Procedures for the Synthesis of Ether Lipids p.391-393, in H. K. Mangold and F. Paltauf, "Ether Lipids", Academic Press, 1983.

Detailed Description Text (49):

The compounds of formula (E) (PG=protecting group=triphenylmethyl, trimethylsilyl, tri-n-propylsilyl, triphenylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl) are known in the literature or are obtainable by art recognized procedures, see T. W. Greene and P. G. Wuts, Protective Groups in Organic Synthesis, p. 68-87, J. Wiley

and Sons; NY, 1991; A. Hermetter and F. Paltauf, Procedures for the Synthesis of Ether Lipids, p. 393 et.seq., in H. K. Mangold and F. Paltauf, "Ether Lipids", Academic Press, 1983; F. Paltauf and A. Hermetter, Methods Enzymol. 197, 134-149 (1991); C. E. Burgos et al, J. Org. Chem. 52, 4973-4977 (1987); P. N. Guvisdalsky and R. Bittman, J. Org. Chem. 54, 4637-4642 (1989).

Detailed Description Text (52):

The protecting group (PG) is removed from compound (F) to yield compound (C) using methods known in the literature or by art recognizable procedures, see A. Hermetter and F. Paltauf, Procedures for the Synthesis of Ether Lipids, P. 393 et.seq., in H. K. Mangold and F. Paltauf, "Ether Lipids", Academic Press, 1983); Y. Rui and D. H. Thompson, J. Org. Chem. 59, 5758-5762 (1994); C. E. Burgos et al., J. Org. Chem. 52, 4973-4977 (1987); and F. Heymans, et al., Biochem. Biophys. Acta 666, 230-237 (1981). ##STR10##

Detailed Description Text (63):

The anti-tumor activity of both naturally and synthetic glycerol-derived ether lipids has been confirmed in the literature, for example, see R. Andreesen, "Ether Lipids in the Therapy of Cancer", Prog. Biochem. Pharmacol., vol.22, pp. 118-131 (Karger, Basel 1988).

Other Reference Publication (1):

Andreesen, R., "Ether Lipids in the Therapy of Cancer," Prog. Biochem. Pharmacol., vol. 22, pp. 118-131 (Kaege, Basal 1988).

Other Reference Publication (7):

Hermetter, A. and Paltauf, F., Procedures for the Synthesis of Ether Lipids, in H.K. Mangold and F. Paltauf, Ether Lipids, Academic Press (1983), p. 393 et.seq.

CLAIMS:

1. Retinoyl substituted glycerophosphoethanolamines of the general Formulas Ia, Ib and Ic: ##STR12## all geometric and optical isomers thereof, and the pharmaceutically acceptable salts of said compounds and isomers, wherein:

R represents a substituted or unsubstituted straight or branched chain C.sub.10-24 alkyl, any such substituent being one or more of halo, C.sub.1-3 alkoxy or cyano;

RET represents a retinoyl ester moiety; and

-OPEA represents a phosphoethanolamine moiety of the formula: ##STR13## wherein R.sub.1 is hydrogen or methyl, provided that at least one R.sub.1 is methyl.

4. A glycerophosphoethanolamine of claim 1, which is of Formula Ia or Formula Ib, or any optical or geometric isomer thereof or pharmaceutically acceptable salt of said compound or isomer, wherein said RET is selected from the group consisting of all-trans-, all-cis-, 9-cis- and 13-cis- retinoyl.

9. A compound of claim 1 which is selected from the group consisting of the optical isomers of 1-O-octadecyl-2-(all-trans-retinoyl)-glycero-3-phosphocholine and the optical isomers of 1-O-n-Octadecyl-3-(all-trans-retinoyl)-glycero-2-phosphocholine.

10. A mixture of compounds, which mixture is selected from the group consisting of a racemic mixture of the optical isomers of 1-O-octadecyl-2-(all-trans-retinoyl)-glycero-3-phosphocholine and a racemic mixture of the optical isomers of 1-O-n-Octadecyl-3-(all-trans-retinoyl)-glycero-2-phosphocholine.

11. A method of treating a solid neoplastic tumor or a leukemia in a mammal afflicted with same comprising administering to said mammal an anti-tumor effective

or anti-leukemia effective amount of a glycerophosphoethanolamine of Formula Ia, Ib, or Ic: ##STR14## or any geometric or optical isomer of any of them, or any pharmaceutically acceptable salt of any of said compounds or isomers thereof, wherein:

R represents a substituted or unsubstituted straight or branched chain C.sub.10-24 alkyl, said substituent being one or more of halo,

C.sub.1-3 alkoxy or cyano;

RET represents a retinoyl ester function; and

-OPEA represent a phosphoethanolamine of the formula: ##STR15## wherein R.sup.1 is hydrogen or methyl, provided that at least one R.sup.1 is methyl.

15. The method of claim 14 wherein what is administered to the mammal is a compound selected from the group consisting of the optical isomers of 1-O-octadecyl-2-(all-trans-retinoyl)-glycero-3-phosphocholine and the optical isomers of 1-O-n-Octadecyl-3-(all-trans-retinoyl)-glycero-2-phosphocholine.

16. The method of claim 15 wherein what is administered to the mammal is a mixture of compounds, which mixture is selected from the group consisting of a racemic mixture of the optical isomers of 1-O-octadecyl-2-(all-trans-retinoyl)-glycero-3-phosphocholine and a racemic mixture of the optical isomers of 1-O-n-octadecyl-3-(all-trans-retinoyl)-glycero-2-phosphocholine.

18. A method of treating psoriasis in a mammal suffering therefrom comprising administering to said human an anti-psoriatic effective amount of a glycerophosphoethanolamine of Formula Ia, Ib or Ic: ##STR16## or any geometric or optical isomer of any of them, or any pharmaceutically acceptable salt of any of said compounds or isomers thereof, wherein:

R represents a substituted or unsubstituted straight or branched chain C.sub.10-24 alkyl, said substituent being one or more of halo, C.sub.1-3 alkoxy or cyano;

RET represents a retinoyl ester function; and

-OPEA represents a phosphoethanolamine of the formula: ##STR17## wherein R.sup.1 is hydrogen or methyl, provided that at least one R.sup.1 is methyl.

22. The method of claim 21 wherein what is administered to the human is a compound selected from the group consisting of the optical isomers of 1-O-octadecyl-2-(all-trans-retinoyl)-glycero-3-phosphocholine and the optical isomers of 1-O-n-octadecyl-3-(all-trans-retinoyl)-glycero-2-phosphocholine.

23. The method of claim 22 wherein what is administered to the human is a mixture of compounds, which mixture is selected from the group consisting of a racemic mixture of the optical isomers of 1-O-octadecyl-2-(all-trans-retinoyl)-glycero-3-phosphocholine and a racemic mixture of the optical isomers of 1-O-n-Octadecyl-3-(all-trans-retinoyl)-glycero-2-phosphocholine.

24. A method of treating inflammation in a mammal suffering therefrom comprising administering to said mammal an anti-inflammation effective amount of a glycerophosphoethanolamine of Formula Ia, Ib or Ic: ##STR18## or any geometric or optical isomer of any of them, or any pharmaceutically acceptable salt of any of said compounds or isomers thereof, wherein:

R represents a substituted or unsubstituted straight or branched chain C.sub.10-24 alkyl, said substituent being one or more of halo, C.sub.1-3 alkoxy or cyano;

RET represents a retinoyl ester function; and

-OPEA represents a phosphoethanolamine of the formula: ##STR19## wherein R.sup.1 is hydrogen or methyl, provided that at least one R.sup.1 is methyl.

28. The method of claim 27 wherein what is administered to the mammal is a compound selected from the group consisting of the optical isomers of 1-O-octadecyl-2-(all-trans-retinoyl)-glycero-3-phosphocholine and the optical isomers of 1-O-n-octadecyl-3-(all-trans-retinoyl)-glycero-2-phosphocholine.

29. The method of claim 28 wherein what is administered to the mammal is a mixture of compounds, which mixture is selected from the group consisting of a racemic mixture of the optical isomers of 1-O-octadecyl-2-(all-trans-retinoyl)-glycero-3-phosphocholine and a racemic mixture of the optical isomers of 1-O-n-Octadecyl-3-(all-trans-retinoyl)-glycero-2-phosphocholine.

31. A pharmaceutical composition comprising (i) an anti-tumor-, anti-psoriatic- or anti-inflammatory-effective amount of a retinoyl substituted glycerophosphoethanolamine of the general Formula Ia, Ib or Ic: ##STR20## or any geometric or optical isomer of any of them, or any pharmaceutically acceptable salt of any of said compounds or isomers thereof, wherein:

R represents a substituted or unsubstituted straight or branched chain C.sub.10-24 alkyl, said substituent being one or more of halo, C.sub.1-3 alkoxy or cyano;

RET represents a retinoyl ester function; and

-OPEA represents a phosphoethanolamine of the formula: ##STR21## wherein R.sup.1 is hydrogen or methyl, provided that at least one R.sup.1 is methyl; and (ii) a pharmaceutically effective carrier.

38. The composition of claim 37 wherein said glycerophosphoethanolamine is a compound selected from the group consisting of the optical isomers of 1-O-octadecyl-2-(all-trans-retinoyl)-glycero-3-phosphocholine and the optical isomers of 1-O-n-octadecyl-3-(all-trans-retinoyl)-glycero-2-phosphocholine.

39. The composition of claim 38 wherein there is a mixture of glycerophosphoethanolamines, said mixture selected from the group consisting of a racemic mixture of the optical isomers of 1-O-octadecyl-2-(all-trans-retinoyl)-glycero-3-phosphocholine and a racemic mixture of the optical isomers of 1-O-n-Octadecyl-3-(all-trans-retinoyl)-glycero-2-phosphocholine.

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L5: Entry 46 of 65

File: USPT

Dec 30, 1997

US-PAT-NO: 5703062

DOCUMENT-IDENTIFIER: US 5703062 A

TITLE: N-het-substituted glycerophosphoethanolamines

DATE-ISSUED: December 30, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Nair; Haridasan K.	Madison	WI		

US-CL-CURRENT: 514/77

CLAIMS:

What is claimed is:

1. An N-Het-substituted glycerophosphoethanolamine of the formula: ##STR4## the isomeric forms thereof, and the pharmaceutically acceptable salts thereof and the isomeric forms; wherein R represents a substituted or unsubstituted straight or branched chain C.sub.14-20 alkyl or alkenyl, said substituent being one or more of halo, C.sub.1-3 alkoxy or cyano, provided that a double bond of said alkenyl does not involve the carbon atom of said alkenyl that is bonded to the oxygen of the glyceryl backbone; and Het represents a 5- to 9-membered monocyclic or bicyclic fused ring system with 1 to 3 heteroatoms, each heteroatom selected from oxygen, sulfur and nitrogen, and provided that Het is not an imidazolinyl ring system.
2. A glycerophosphoethanolamine of claim 1 wherein R is C.sub.16-18 alkyl or alkenyl.
3. A glycerophosphoethanolamine of claim 1 wherein Het is 2-thiazolinyl.
4. A glycerophosphoethanolamine of claim 1 wherein R is C.sub.18 alkyl and Het is 2-thiazolinyl.
5. A method of inhibiting cell growth of a solid tumor in a mammal afflicted with same which comprises administering to said mammal an anti-tumor effective amount of an N-Het-substituted glycerophosphoethanolamine of the formula: ##STR5## an isomeric form thereof, or a pharmaceutically acceptable salt of either; wherein R represents a substituted or unsubstituted straight or branched chain C.sub.14-20 alkyl or alkenyl, said substituent being one or more of halo, C.sub.1-3 alkoxy or cyano, provided that a double bond of said alkenyl does not involve the carbon atom of said alkenyl that is bonded to the oxygen of the glyceryl backbone; and Het represents a 5- to 9-membered monocyclic or bicyclic fused ring system with 1 to 3 heteroatoms, each heteroatom selected from oxygen, sulfur and nitrogen, and provided that Het is not an imidazolinyl ring system.

6. A method of claim 5 wherein, in the glycerophosphoethanolamine, R is C.sub.16-18 alkyl or alkenyl.

7. A method of claim 5 wherein, in the glycerophosphoethanolamine, Het is 2-thiazolinyl.

8. A method of claim 5 wherein, in the glycerophosphoethanolamine, R is C.sub.18 alkyl and Het is 2-thiazolinyl.

9. A method of treating psoriasis in a mammal afflicted with same which comprises administering to said mammal an anti-psoriatic effective amount of an N-Het-substituted glycerophosphoethanolamine of the formula: ##STR6## an isomeric form thereof, or a pharmaceutically acceptable salt of either; wherein R represents a substituted or unsubstituted straight or branched chain C.sub.14-20 alkyl or alkenyl, said substituent being one or more of halo, C.sub.1-3 alkoxy or cyano, provided that a double bond of said alkenyl does not involve the carbon atom of said alkenyl that is bonded to the oxygen of the glyceryl backbone; and Het represents a 5- to 9-membered monocyclic or bicyclic fused ring system with 1 to 3 heteroatoms, each heteroatom selected from oxygen, sulfur and nitrogen, and provided that Het is not an imidazolinyl ring system.

10. A method of claim 9 wherein, in the glycerophosphoethanolamine, R is C.sub.16-18 alkyl or alkenyl.

11. A method of claim 9 wherein, in the glycerophosphoethanolamine, Het is 2-thiazolinyl.

12. A method of claim 9 wherein, in the glycerophosphoethanolamine, R is C.sub.18 alkyl and Het is 2-thiazolinyl.

13. A method of treating inflammation in a mammal afflicted with same which comprises administering to said mammal an anti-inflammatory effective amount of an N-Het-substituted glycerophosphoethanolamine of the formula: ##STR7## an isomeric form thereof, or a pharmaceutically acceptable salt of either; wherein R represents a substituted or unsubstituted straight or branched chain C.sub.14-20 alkyl or alkenyl, said substituent being one or more of halo, C.sub.1-3 alkoxy or cyano, provided that a double bond of said alkenyl does not involve the carbon atom of said alkenyl that is bonded to the oxygen of the glyceryl backbone; and Het represents a 5- to 9-membered monocyclic or bicyclic fused ring system with 1 to 3 heteroatoms, each heteroatom selected from oxygen, sulfur and nitrogen, and provided that Het is not an imidazolinyl ring system.

14. A method of claim 13 wherein, in the glycerophosphoethanolamine, R is C.sub.16-18 alkyl or alkenyl.

15. A method of claim 13 wherein, in the glycerophosphoethanolamine, Het is 2-thiazolinyl.

16. A method of claim 13 wherein, in the glycerophosphoethanolamine, R is C.sub.18 alkyl and Het is 2-thiazolinyl.

17. A method of inhibiting PAF activity in a host mammal having a PAF-induced pathophysiological condition comprising administering to said mammal an effective PAF antagonist amount of an N-Het-substituted

glycerophosphoethanolamine of the formula: ##STR8## an isomeric form thereof, or a pharmaceutically acceptable salt of either; wherein R represents a substituted or unsubstituted straight or branched chain C.sub.14-20 alkyl or alkenyl, said substituent being one or more of halo, C.sub.1-3 alkoxy or cyano, provided that a double bond of said alkenyl does not involve the carbon atom of said alkenyl that is bonded to the oxygen of the glyceryl backbone; and Het represents a 5- to 9-membered monocyclic or bicyclic fused ring system with 1 to 3 heteroatoms, each heteroatom selected from oxygen, sulfur and nitrogen, and provided that Het is not an imidazolinyl ring system.

18. A method of claim 17 wherein, in the glycerophosphoethanolamine, R is C.sub.16-18 alkyl or alkenyl.

19. A method of claim 17 wherein, in the glycerophosphoethanolamine, Het is 2-thiazolinyl.

20. A method of claim 17 wherein, in the glycerophosphoethanolamine, R is C.sub.18 alkyl and Het is 2-thiazolinyl.

21. A pharmaceutical composition comprising an effective anti-tumor, anti-psoriatic, anti-inflammatory or PAF antagonist amount of an N-Het-substituted glycerophosphoethanolamine of the formula: ##STR9## an isomeric form thereof, or a pharmaceutically acceptable salt of either; wherein R represents a substituted or unsubstituted straight or branched chain C.sub.14-20 alkyl or alkenyl, said substituent being one or more of halo, C.sub.1-3 alkoxy or cyano, provided that a double bond of said alkenyl does not involve the carbon atom of said alkenyl that is bonded to the oxygen of the glyceryl backbone; and Het represents a 5- to 9-membered monocyclic or bicyclic fused ring system with 1 to 3 heteroatoms, each heteroatom selected from oxygen, sulfur and nitrogen, and provided that Het is not an imidazolinyl ring system; and the pharmaceutically acceptable salts thereof; and a pharmaceutically acceptable carrier.

22. The composition of claim 21 wherein R is C.sub.16-18 alkyl or alkenyl.

23. The composition of claim 21 wherein Het is 2-thiazolinyl.

24. The composition of claim 21 wherein R is C.sub.18 alkyl and Het is 2-thiazolinyl.

25. The composition of claim 21 in unit dosage form as a tablet or capsule containing from about 0.5 to about 500 mg of said N-Het-Substituted glycerophosphethanolamine, isomeric form thereof or salt thereof.

26. The composition of claim 21 suitable for oral administration.

27. The composition of claim 21 suitable for parenteral administration.

28. The composition of claim 21 suitable for topical administration.

29. The composition of claim 21 suitable for inhalation administration.

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L5: Entry 53 of 65

File: USPT

Aug 22, 1995

DOCUMENT-IDENTIFIER: US 5444052 A

TITLE: Amphotericin B composition with enhanced fungal activity

Detailed Description Text (4):

Included in the scope of the present invention are all glycerol ethers according to the above formulae, including all optical and geometric isomers satisfying the formulae, and all racemic, diastereomeric or other mixtures of any such isomers. The 1-glycerol ethers are optically active. According to the 1976 Recommendations for The Nomenclature of Lipids, IUPAC-IUB Commission on Biochemical Nomenclature, reported at Lipids 12, 455-468 (1977), carbon atoms of glycerol are numbered stereospecifically. The carbon atom that appears on top in a Fischer projection showing a vertical carbon chain with the C-2 hydroxyl to the left is designated as C-1. To differentiate such numbering from conventional numbering conveying no steric information, the prefix "sn" (for stereospecifically numbered) is used. The prefix "rac" (for racemo) is an equal mixture of both antipodes. According to this convention, the two optical isomers of 1-O-dodecylglycerol are designated as "sn-1-O-dodecylglycerol" and "sn-3-O-dodecylglycerol". The corresponding racemate is designated "rac-1-O-dodecylglycerol".

Detailed Description Text (8):

According to the present invention, the glycerol ether and amphotericin B are administered to a mammal, particularly a human being, in amounts sufficient to treat fungal infection. The amount of each drug may vary according to the size, weight, age and sex of the infected individual; whether the treatment is prophylactic or therapeutic; the nature, stage and extent of the infection; the identity of the infecting organism; the route of administration; and other factors. For intravenous administration, the dosage should be adjusted to the requirements of each patient since tolerance to amphotericin B varies. The amount of amphotericin B administered intravenously preferably ranges from about 0.01 to about 1.5 mg per kg of the weight of the individual undergoing treatment, per day. More preferably, the amount is from about 0.025 to about 1.0 mg/kg, most preferably 0.3 to 0.7 mg/kg per day. At an amphotericin B dosage of 1 mg/kg, peak serum concentrations of about 2-3 micrograms/ml are achieved by the end of infusion, and typically remain above 0.5 micrograms/ml for up to 24 hours thereafter. The amount of glycerol ether lipid is any amount which is useful in potentiating the antifungal activity of the amphotericin B. While it is preferred that the two drugs be administered simultaneously, such as in the form of a single pharmaceutical composition, the two agents may also be administered separately, in sequence.

Detailed Description Text (19):

Lack of growth and viability of *C. neoformans* at graded concentrations of rac-1-O-dodecylglycerol and amphotericin B (Sigma Chemical Co.: 45% amphotericin B, 35% sodium deoxycholate, 20% sodium phosphate), separately and combined, was determined by the "checkerboard" technique of Krogstad et al., Fundamentals of Medical Bacteriology and Mycology (2nd Ed.) 521-525, 544-550 (1980). Briefly, the growth of the fungi was measured in 96 well microtiter plates. A growth medium (100 .mu.l per well) containing graded combinations of DDG and amphotericin B was inoculated with 5 .mu.l of log phase culture of 0.1 optical density at a wavelength of 675 nm. The growth inoculum was measured turbidimetrically. Growth or no growth of each microtiter plate well was determined visually after 24 hours of continual shaking

and aeration (microtiter plate analysis). To ensure single cell death, each well visually exhibiting no apparent growth was plated on 2% agar, 1% bactopectone, 2% glucose plates, incubated at 37.degree. C. for 24 hours and analyzed for growth (agar plate analysis). The data are set forth in FIG. 1 (25.degree. C. incubation followed by microtiter plate analysis (.increment.)) and agar plate analysis (.) and FIG. 3 (37.degree. C. incubation followed by microtiter analysis (.quadrature.) and agar plate analysis (.) . Each graph represents an average of three separate trials. The steep hyperbolic curves generated from these data are indicative of strong synergism between amphotericin B and DDG against C. neoformans. Synergy is defined as no growth of fungi in the presence of the two antifungal agents, each of which is present at a concentration less than one-half of its MIC. As seen in Table 1, at 25.degree. C. and one-half the MIC for rac-1-DDG (7.5 microgram/ml) the MIC for amphotericin B dropped to 0.047 micrograms/ml from 2.25 micrograms/ml. This represents a 48-fold decrease in the amphotericin B MIC. With amphotericin B present at one-half of its MIC (1.12 micrograms/ml) the rac-1-DDG MIC dropped to 0.125 micrograms/ml, a 120-fold decrease. Viability studies (data not shown) showed that the yeast was killed and not just growth-inhibited by DDG and amphotericin B.

Detailed Description Text (30):

The steep hyperbolic curves are indicative of strong synergism between amphotericin B and the glycerol ether. The substantial overlap of curves in FIGS. 11 and 12 indicates that the two 1-DDG optical isomers are substantially equivalent in potentiating the antifungal activity of amphotericin B, and that the 1-DDG optical isomers are substantially equivalent in this respect to the 2-DDG position isomer.

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